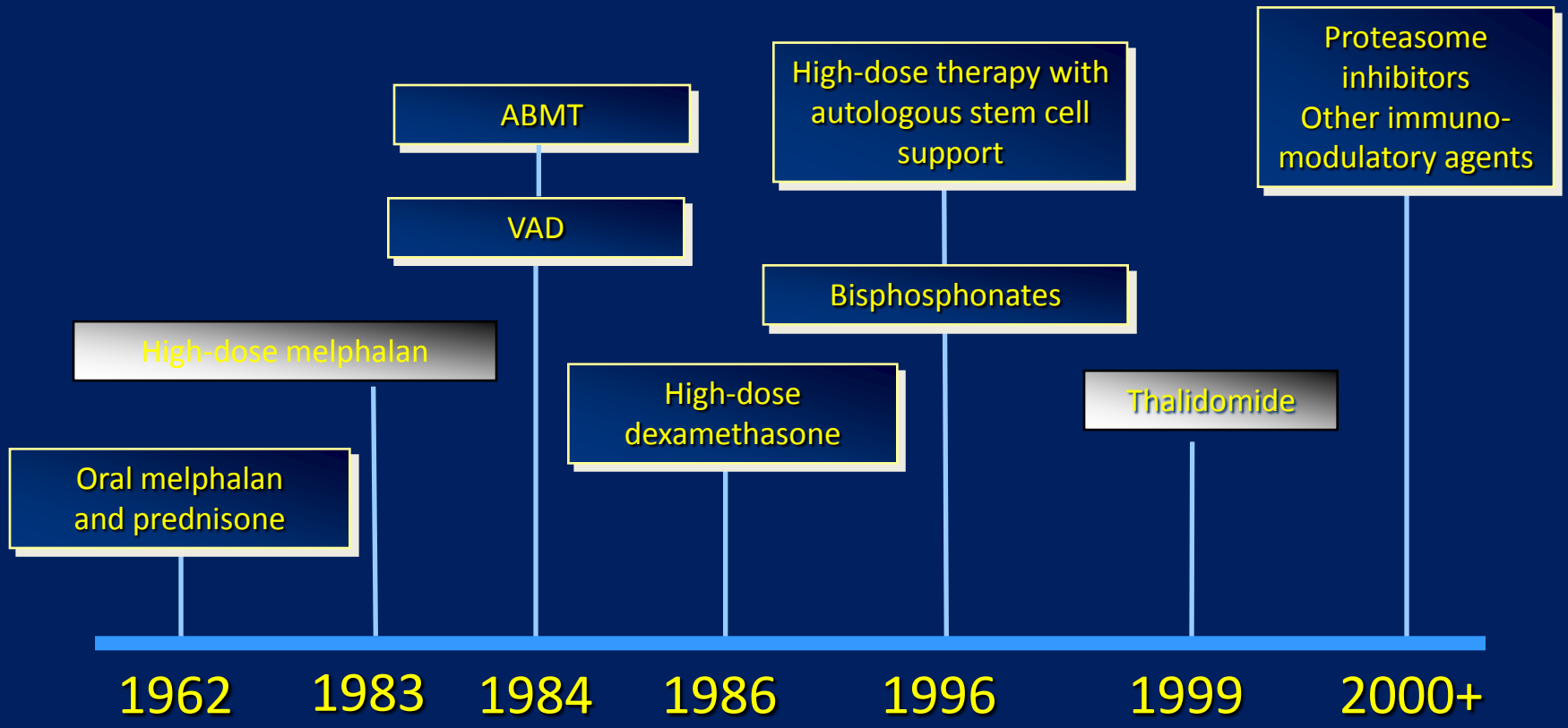
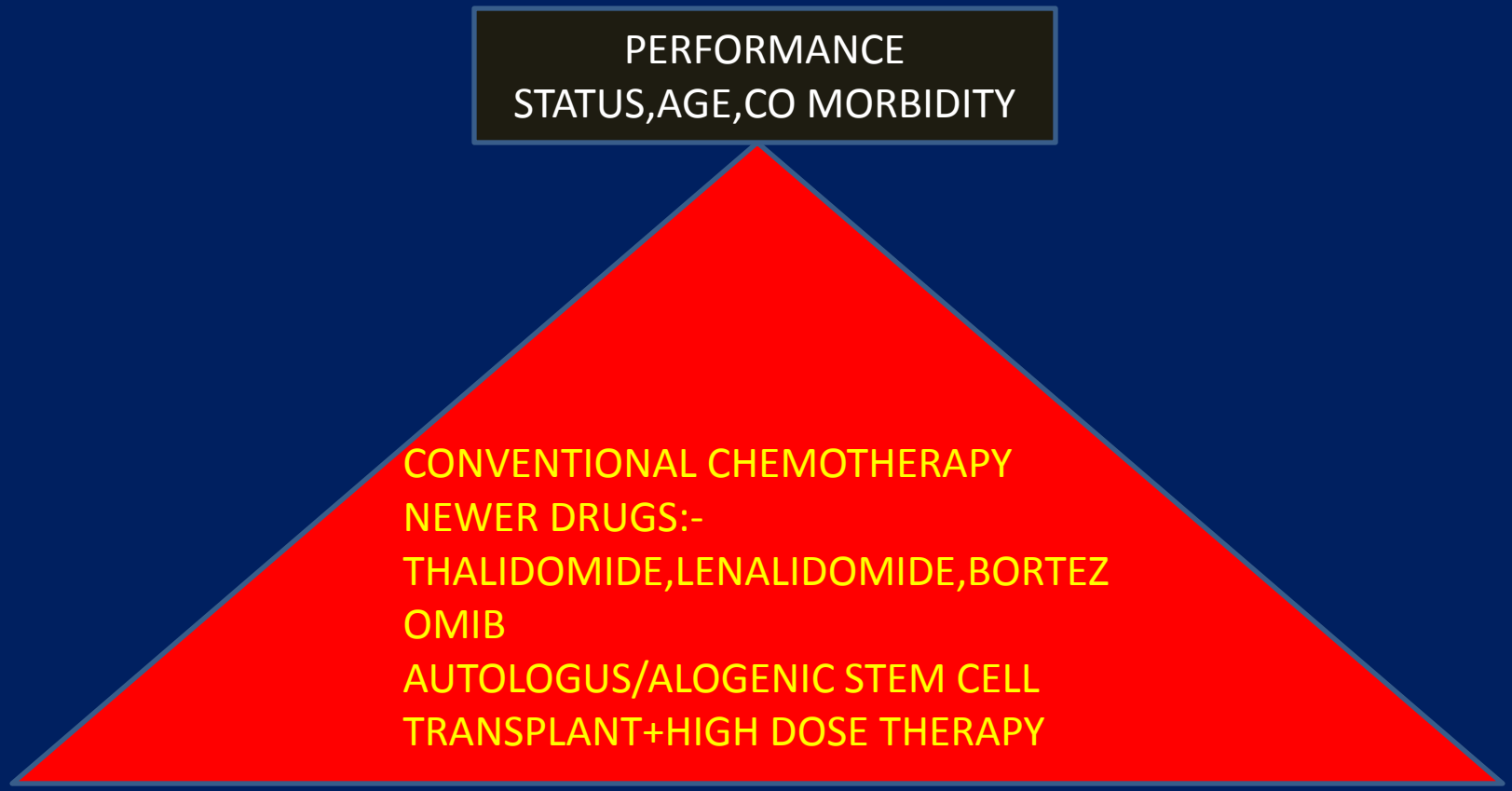
HISTORICAL PERSPECTIVE OF MULTIPLE MYELOMA



Barlogie B et al. *N Engl J Med*. 1984;310:1353; Berenson JR et al. *N Engl J Med*. 1996;334:488; Alexanian R et al. *Ann Intern Med*. 1986;105:8; Bergsagel D. *Cancer Chemother Rep*. 1962;21:87; Salmon SE et al. *Cancer Chemother Rep*. 1967;51:179; Rousselot P et al. *Cancer Res*. 1999;59:1041;McElwainTJ, Powles RL. *Lancet.* 1983;2:822

TREATMENT APPROACH BASED ON



EUROPEAN BLOOD AND MARROW TRANSPLANTATION GROUP

	CR	PR	MR	NO CHANGE	PROGRESSIVE DISEASE (REQUIRE 1/MORE)	RELAPSE (REQUIRE ATLEAST 1 OF FOLLOWING)
MONOCLONAL PROTEIN FROM BLOOD-2 DETERMINATION FOR 6 WEEKS	DISAPPEAR -2 DETERMINATION FOR 6 WEEKS	>50% REDN	>25% TO 49% REDN	NOT MEETING THE CRITERIA OF MR/PD	>25% INCREASE,ABSOLUTE INCREASE OF AT LEAST 5 G/L	REAPPEARANCE
URINARY LIGHT CHAIN(24 HRS) -2 DETERMINATION FOR 6 WEEKS	DISAPPEAR	>90% REDN OR < 200 MG	50-89% OR >200 MG		>25% INCREASE,ABSOLUTE INCREASE OF AT LEAST 5 G/L OR >200 MG/24 HRS	
PLASMA CELL IN B.M	< 5%				>25% INCREASE,ABSOLUTE INCREASE OF 10%	>5%
LYTIC BONE LESION	NO INCREASE IN SIZE/NUMBER	NO INCREASE IN SIZE/NUMBER	NO INCREASE IN SIZE/NUMBER		INCREASE IN SIZE	NEW LESION/INCREASE SIZE OF LESION
SOFT TISSUE PLASMACYTOMA	DISAPPEAR AT LEAST FOR 6 WKS	>50% REDN	25 TO 49%		NEW BONE LESION/SOFT TISSUE, HYPERCALCEMIA	NEW LESION/INCREASE SIZE OF LESION HYPERCALCEMIA

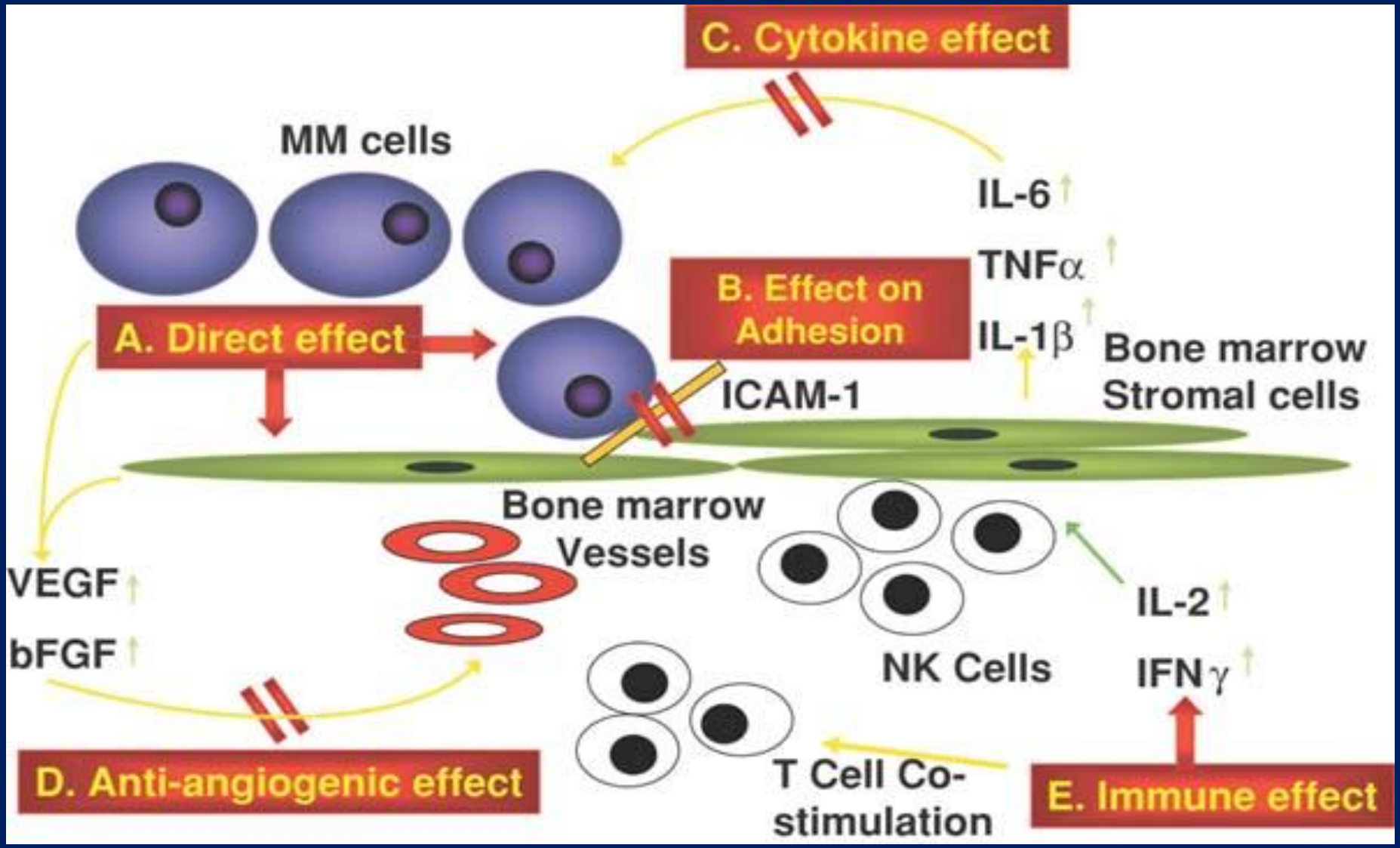
nCR:-same as CR but immunofixation shows monoclonal protein

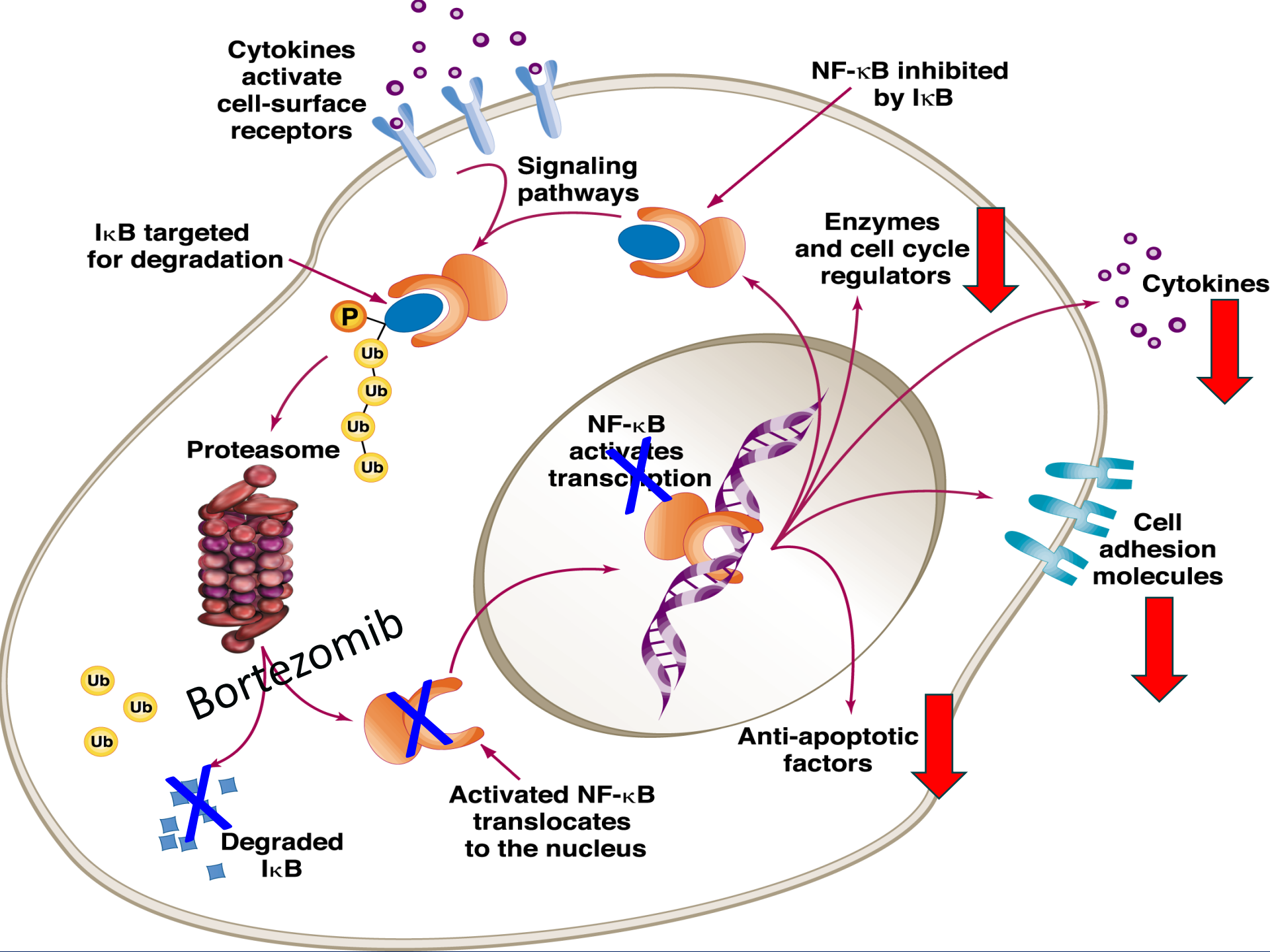
INTERNATIONAL MYELOMA WORKING GROUP UNIFORM RESPONSE CRITERIA

- ***STRINGENT COMPLETE RESPONSE***:-CR+NORMAL FREE LIGHT CHAIN ASSAY RATIO+ABSENCE OF CLONAL CELLS IN BONE MARROW BY IHC
- ***COMPLETE RESPONSE***:-NEGATIVE IMMUNOFIXATION ON SERUM & URINE AND DISSAPEARANCE OF ANY SOFT TISSUE PLASMACYTOMA & <5% PLASMA CELL IN BONE MARROW
- ***VERY GOOD PARTIAL RESPONSE(vgpr)***:-SERUM AND URINE M PROTEIN DETECTABLE BY IMMUNOFIXATION BUT NOT ON ELECTROPHORESIS, OR >/= 90% REDUCTION IN SERUM M PROTEIN + URINARY M PROTEIN(< 100 MG/24 Hrs)
- ***PARTIAL RESPONSE***:-> 50% DECREASE IN SERUM M PROTEIN & DECREASE IN 24 HRS URINE M PROTEINBY 90% OR TO <200MG/24 HRS

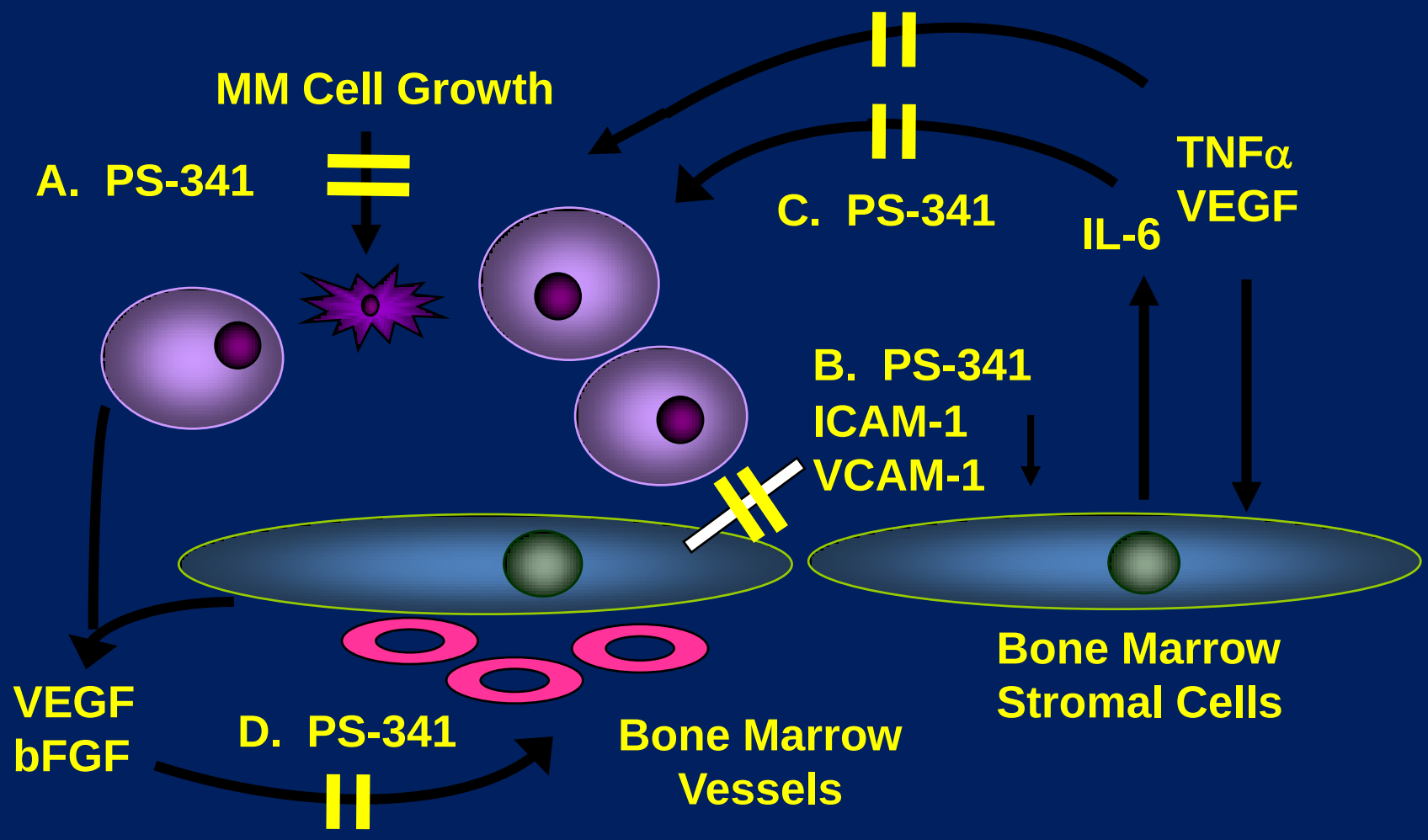
  - NON SECRETORY MYELOMA:->50% DECREASE IN DIFFERENCE BETWEEN INVOLVED AND UN INVOLVED FREE CHAIN LEVELS.IF SERUM AND URINE PROTEIN,FLC NOT MEASURES>50% DECREASE IN PLASMACELL IN BONE MARROW OF >30%

EFFECTS OF THALIDOMIDE




Cytokines activate cell-surface receptors
NF-κB inhibited by IκB
Signaling pathways
IκB targeted for degradation
P
Ub
Ub
Ub
Ub
Proteasome
Enzymes and cell cycle regulators
Cytokines
NF-κB activates transcription
Cell adhesion molecules
Bortezomib
Ub
Ub
Ub
Anti-apoptotic factors
Activated NF-κB translocates to the nucleus
Degraded IκB

Bortezomib: Mechanism of Action in MM



Hideshima et al. *Cancer Res* 61: 3071, 2001
Hideshima et al. *Oncogene* 20: 4519, 2001

Mitsiades et al. *Blood* 99: 4079, 2002
Hideshima et al. *J Biol Chem* 277: 16639, 2002

GENERAL TREATMENT APPROACH

<table>
<tr><td rowspan="6">HSCT available and appropriate</td><td rowspan="6">Induction therapy

No Alkylator Dex/Thal+ Dex/VAD</td><td rowspan="6">Stem cell collection</td><td rowspan="2">Autograft 1</td><td rowspan="2">Autograft 2</td><td>Maintenance</td><td rowspan="6">Salvage therapy</td></tr>
<tr><td>Observation</td></tr>
<tr><td colspan="2" rowspan="2">Autograft</td><td>Maintenance</td></tr>
<tr><td>Observation</td></tr>
<tr><td>Maintenance</td><td rowspan="2">Autograft</td><td>Maintenance</td></tr>
<tr><td>Observation</td><td>Observation</td></tr>
<tr><td rowspan="2">HSCT not available or appropriate</td><td rowspan="2">Induction therapy</td><td colspan="5">Maintenance</td><td rowspan="2">Salvage therapy</td></tr>
<tr><td colspan="5">Observation</td></tr>
</table>

Abella. *Oncology News International.* 2007;16:27; Barlogie et al. In: *Williams Hematology.* 7th ed. 2006:1501; Durie et al. *Hematol J*. 2003;4:379; MMRF. *Multiple Myeloma: Disease Overview*. 2006. www.multiplemyeloma.org; Rajkumar et al. *Blood*. 2005;106(3):812.

Risk-adapted Therapy in MM

mSMART : Classification of Active MM

High-Risk (25%)

FISH

- **Del 17p-**
- **t(4;14)**
- **t(14;16)**

Cytogenetic Deletion 13

Cytogenetic Hypodiploidy

PCLI ≥ 3%

Standard-Risk (75%) **

All others including:

- **Hyperdiploid**
- **t(11;14)**
- **t(6;14)**

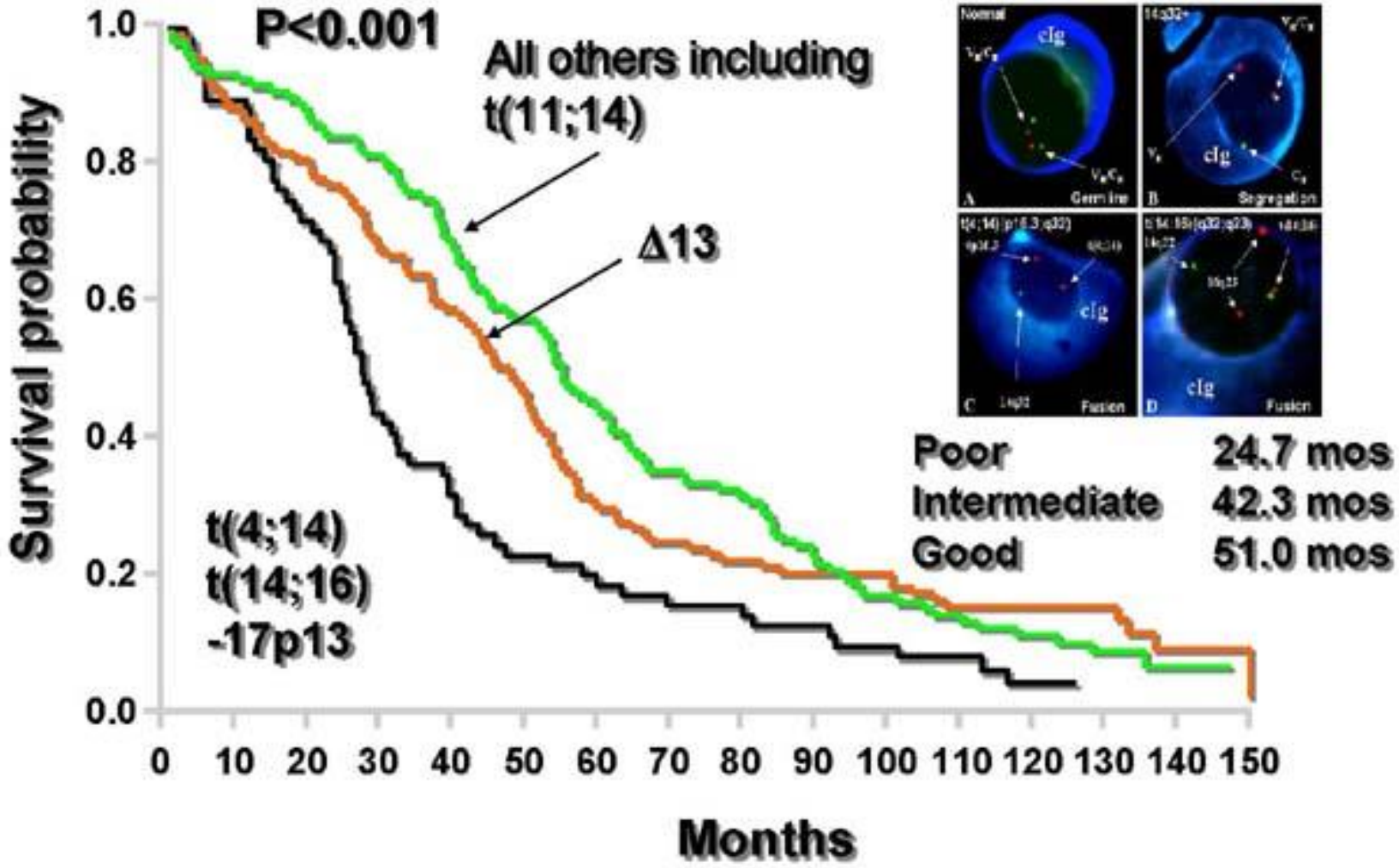
****Low risk with β-2 microglobulin > 5.5 (in absence of renal failure)or LDH >upper limit of normal may be at higher risk.**

Mayo Clin Proc 2007;82:323-341

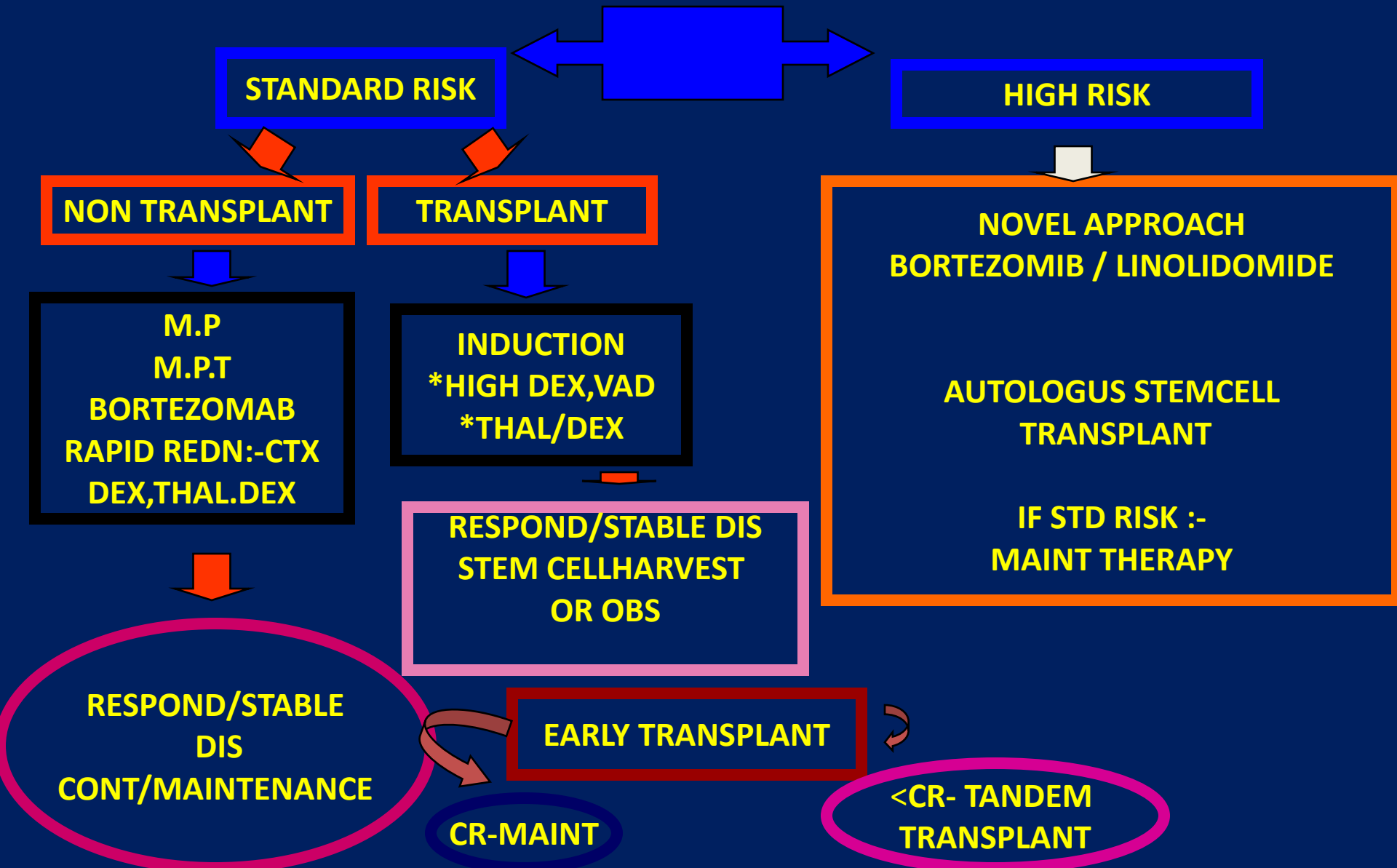
Clinical and biologic implications of recurrent genomic aberrations in myeloma

Rafael Fonseca, Emily Blood, Montserrat Rue, David Harrington, Martin M. Oken, Robert A. Kyle, Gordon W. Dewald, Brian Van Ness, Scott A. Van Wier, Kimberly J. Henderson, Richard J. Bailey, and Philip R. Greipp

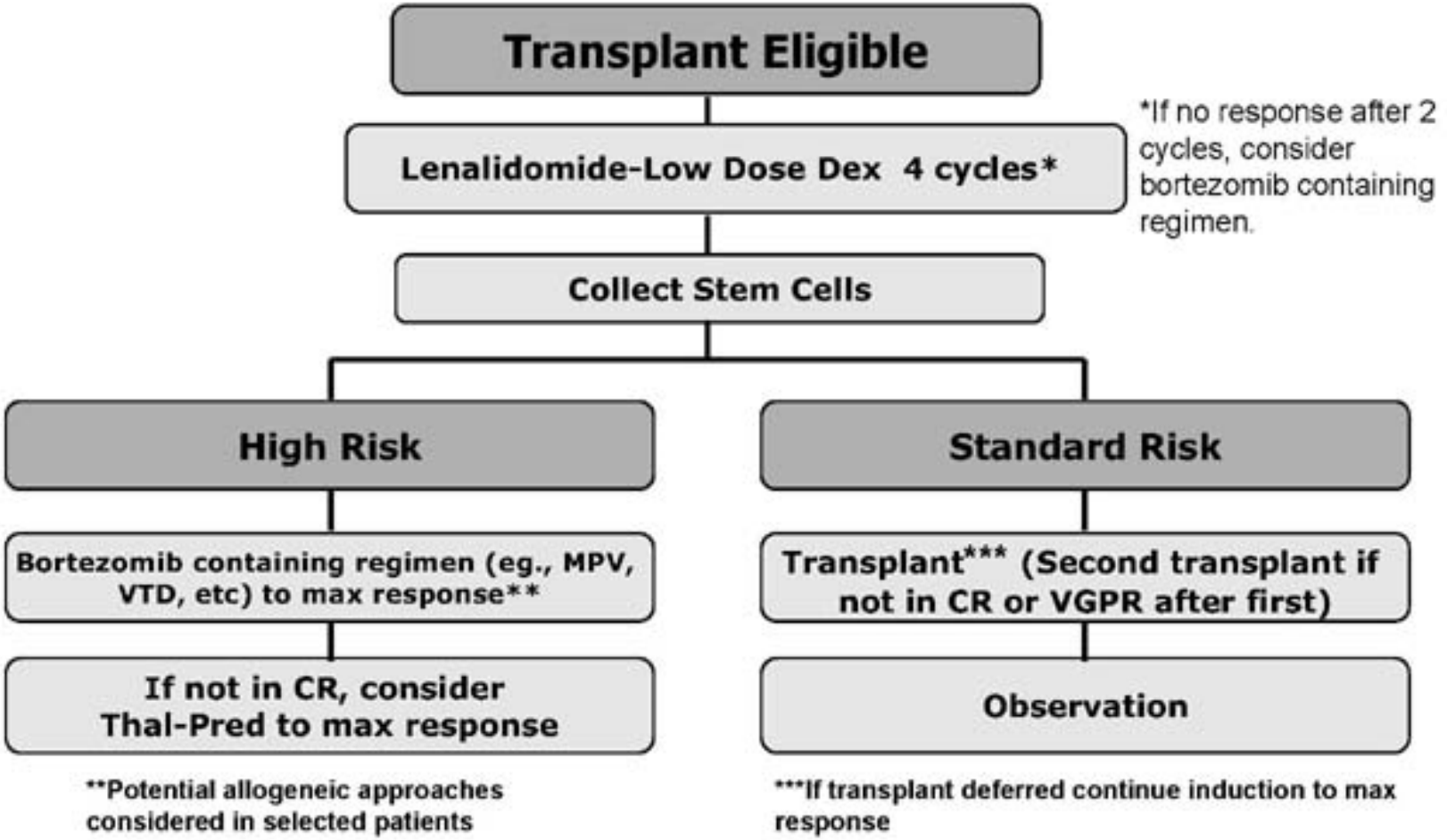
Blood 2003



RISK STRATIFICATION



mSMART – off-study



DRUG	DOSE	CR + PR	MED.DURATION OF RESPONSE	O.S	
MP	8MG/M2 60MG/M2 D1-4	3%+50%	18 MO	24-36 MO	SHOULD NOT USED AS INDN IN SCT
VAD	V-.4MG/D D-9MG/M2/D D40MG/M2 D1-4	27%+57%	0.9 mo	36 MO	
THALIDOMIDE	200MG/DAY		MED TIME TO PROGRESSION:- 14.5 MO	EVENT FREE SURV- 3MO	
DEXA	20MG/M2 40MG/M2 D1-4,9-1217- 20,EVERY 35 DAYS	37%-51%			
BORTEZOMIB DEXA	1.3MG/M2D1,D4,D8, D11 20MGD1,2,4,5,8,9, 11,12		12 MO		
DVD	D40MG/M2 D1,VCR- 2MG D1,DEXA- 40MG,D1-4		MEDIAN TIME TO PROGRESSION- 23.1 MO		

Melphalan/Prednisone Treatment

- Alkylating agent + corticosteroid dosing
  - Dosing: 0.25 mg/kg/day melphalan for 4 days + 20 mg prednisone tid for 6 days
  - Duration: every 4 to 6 wk
- 40% remission (at least 75% reduction in serum myeloma protein, 95% reduction in Bence Jones proteinuria and >5% marrow plasma cells)

Alexanian R et al. *JAMA*. 1969;208:680
Dimopoulos. *NEJM*. 1994;330;7;484

Melphalan/Prednisone Treatment

- Median duration of remission about 2 years
- Median survival–3 years
- <10% live longer than 10 years
- NO evidence of disease cured
- Drug resistance is an issue
- Not recommended for candidates for SCT
- Full benefit takes several months

Alexanian R et al. *JAMA.* 1969;208:680
Dimopoulos *N Engl J Med.* 1994;330:7-484
http:/Myeloma.org

VAD

- Dosing
  - Vincristine: 0.4 mg/day IV daily for 4 days
  - Doxorubicin: 9 mg/m^2/day IV daily for 4 days
  - Dexamethasone: 40 mg po days 1–4, 9–12, 17–20
  - Repeat cycle q 28 days $\times$ 4 cycles
- Reduction in tumor mass: $>$75% in 70% pts
- Remission: 70% pts
- Median time to response: 0.9 mo
- Can be used prior to SCT

Barlogie B et al. *N Engl J Med.* 1984;310:1353
http;//myeloma.org/

DVd versus VAD in Newly Diagnosed Myeloma

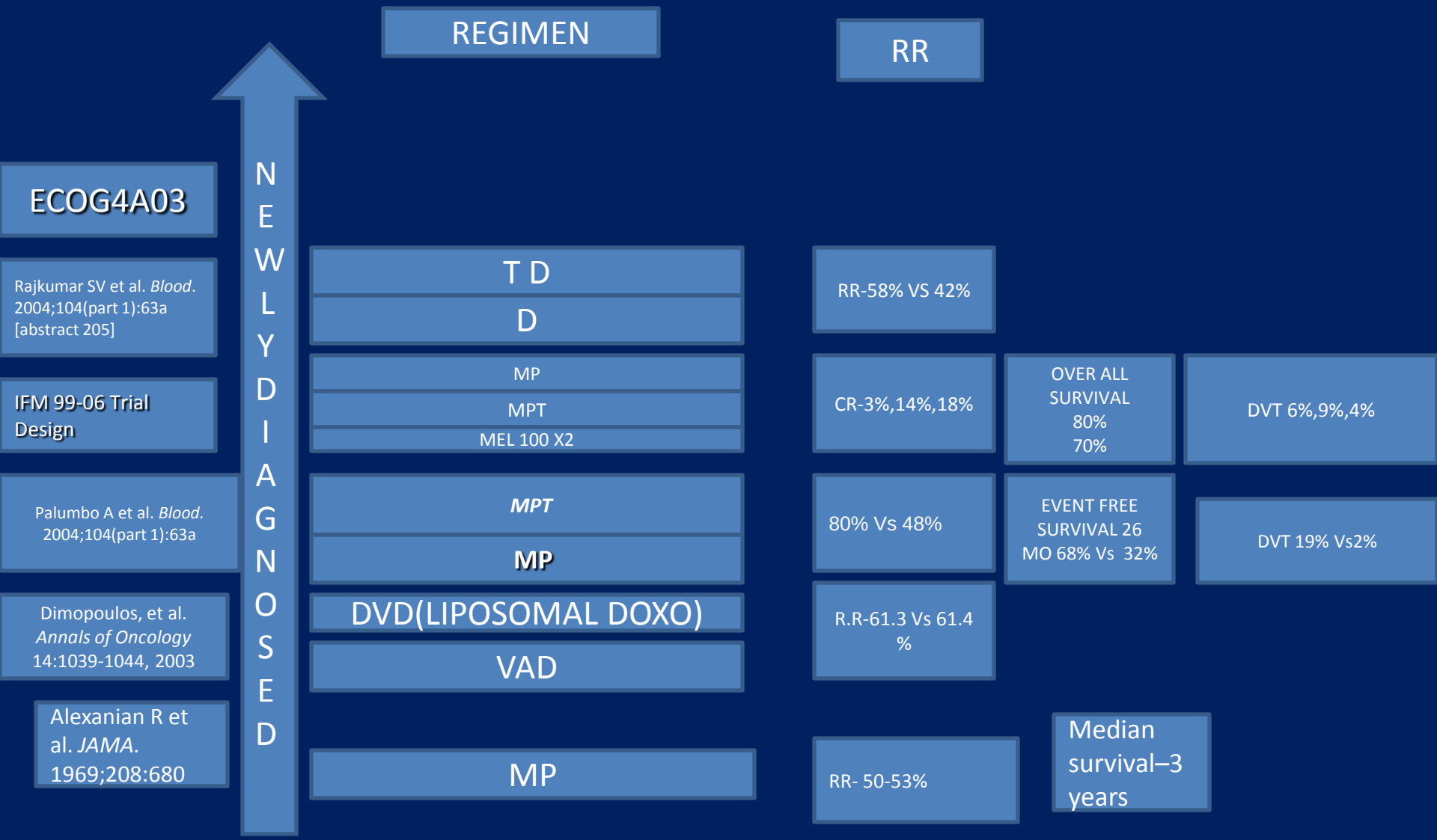
261 pts

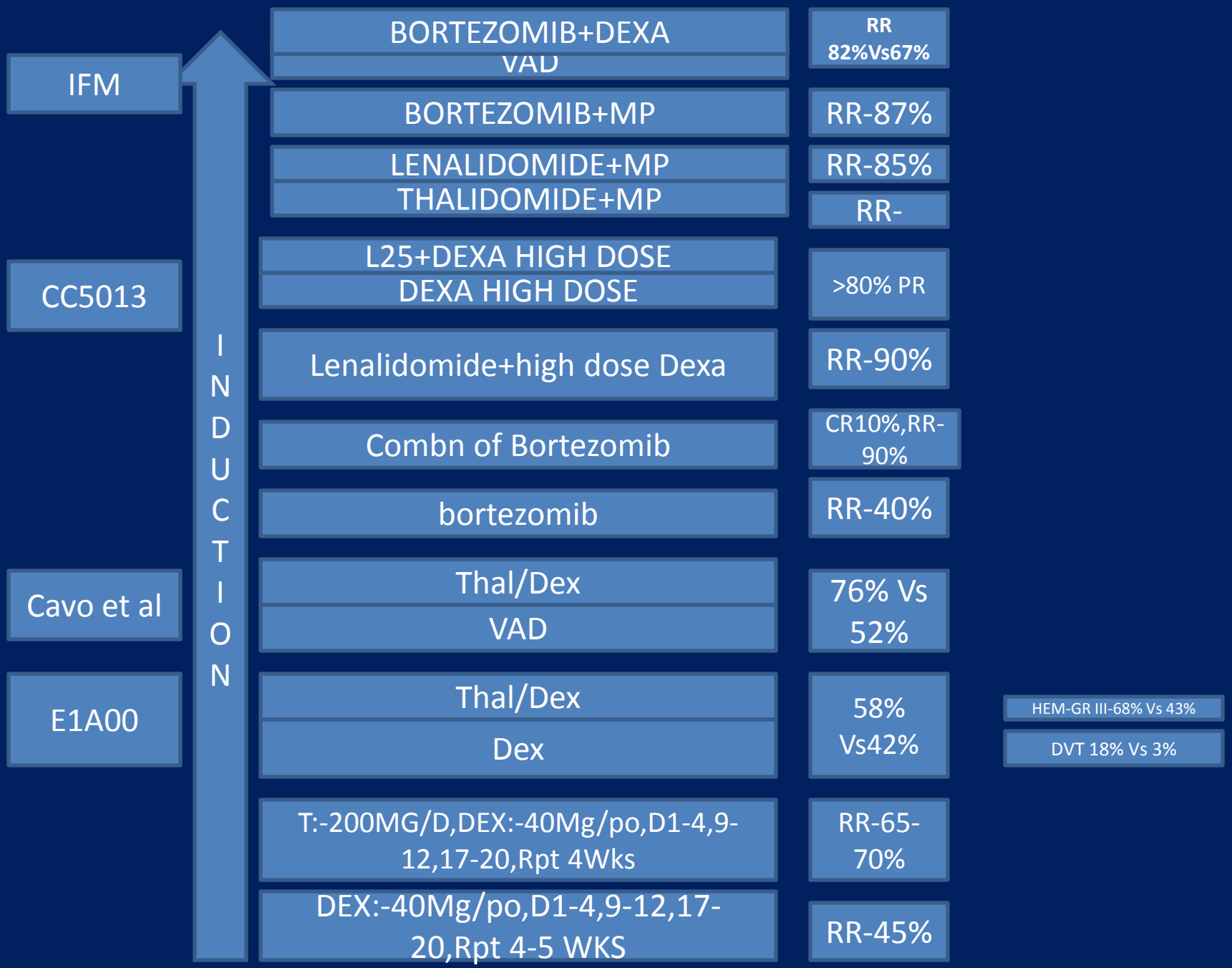
Randomized trial

- Liposomal doxorubicin used instead of adriamycin in the VAD regimen
- Response rate:
  - 61.3% with DVd
  - 61.4% with VAD
- Toxicities were mild or moderate and equally distributed between the two treatment arms with the exception of alopecia, which was more common in VAD arm, and of palmar–plantar erythrodysesthesia, which was more common in DVd arm.

Dimopoulos, et al. *Annals of Oncology* 14:1039-1044, 2003

- DESPITE BETTER RESPONSE RATE,NO SURVIVAL BENEFIT HAS SHOWN WITH MORE AGGRESSIVE COMBINATION CT AS COMPARED TO MP.
- IF IMMIDIATE CYTO REDUCTION IS ESSENTIAL (for renal failure or lytic bone lesion):-COMBINATION OF VBMCP(vcr,carmustine,mel,ctx,pdn)


REGIMEN
RR
NEWLY DIAGNOSED
ECOG4A03
Rajkumar SV et al. *Blood*. 2004;104(part 1):63a [abstract 205]
IFM 99-06 Trial Design
Palumbo A et al. *Blood*. 2004;104(part 1):63a
Dimopoulos, et al. *Annals of Oncology* 14:1039-1044, 2003
Alexanian R et al. *JAMA*. 1969;208:680
T D
D
MP
MPT
MEL 100 X2
MPT
MP
DVD(LIPOSOMAL DOXO)
VAD
MP
RR-58% VS 42%
CR-3%,14%,18%
OVER ALL SURVIVAL 80% 70%
DVT 6%,9%,4%
80% Vs 48%
EVENT FREE SURVIVAL 26 MO 68% Vs 32%
DVT 19% Vs2%
R.R-61.3 Vs 61.4 %
RR- 50-53%
Median survival–3 years


IFM
CC5013
Cavo et al
E1A00
INDUCTION
BORTEZOMIB+DEXA
VAD
RR 82%Vs67%
BORTEZOMIB+MP
RR-87%
LENALIDOMIDE+MP
RR-85%
THALIDOMIDE+MP
RR-
L25+DEXA HIGH DOSE
DEXA HIGH DOSE
>80% PR
Lenalidomide+high dose Dexa
RR-90%
Combn of Bortezomib
CR10%,RR-90%
bortezomib
RR-40%
Thal/Dex
VAD
76% Vs 52%
Thal/Dex
Dex
58% Vs42%
HEM-GR III-68% Vs 43%
DVT 18% Vs 3%
T:-200MG/D,DEX:-40Mg/po,D1-4,9-12,17-20,Rpt 4Wks
RR-65-70%
DEX:-40Mg/po,D1-4,9-12,17-20,Rpt 4-5 WKS
RR-45%

Transplant Candidates: Most Commonly Used Induction Regimens

VAD

- Cumbersome
- Toxicity
- 55-65% RR
- 85% of effect secondary to Dex

Dexamethasone

- Oral
- Less toxicity than VAD or Thal/Dex
- 43% RR

Thal/Dex

- Oral
- Increased toxicity compared to Dex
- 64-72% RR

Transplant candidates should not receive alkylator-based therapy

Alexanian R. *Blood*. 1992;80:887-890; Anagnostopoulos ASH 2001
Rajkumar SV. *JCO* 2002; Weber *JCO* 2003
Rajkumar, et al. *Blood* 2004: 104 (part 1):63a (abstract 205)

TABLE 54.8B Thalidomide Regimens in Newly Diagnosed Multiple Myeloma

Study	*Phase*	*N*	*Regimen*	*CR/VGPR*	*CR + PR*	*1-yr Survival*	*Reference*
Rajkumar (Mayo)	II	50	Thal + Dex	N/R	64%	N/R	*JCO* 2002
Weber (MDACC)	II	28	Thal	N/R	36%	N/R	*JCO* 2003
		40	Thal + Dex	16%	72%		
Cavo	II	71	Thal + Dex	17%	66%	N/R	*Hematologica* 2004
Rajkumar, E1A00	III	103	Thal + Dex	4% (CR)	63%	80%	*JCO* 2006
Rajkumar, MM003	III	470	Thal + Dex	44%	69%	80%	ASH 2006
Palumbo	III	129	MP-T	36%	76%	87%	*Lancet* 2006
Facon	III	124	MP-T	50%	81%	88%	ASCO 2006
Barlogie	III	323	TT2 + Thal	69%	83%	92%	*NEJM* 2006
Goldschmidt	III	203	TAD	7%	80%	N/R	ASH 2005
Offidani	II	50	ThaDD (Thal + PLD + Dex)	56%	84%	89%	*Blood* 2006
Borrello	II	27	Thal + Bort	22%	82%	N/R	ASH 2006
Wang	II	36	Thal + Bort + Dex (VTD)	19%	92%	N/R	ASH 2005

TABLE 54.9B Lenalidomide Regimens in Newly Diagnosed Multiple Myeloma

Study	*Phase*	*N*	*Regimen*	*CR/VGPR*	*CR + PR*	*1-yr Survival Rate*	*Reference*
Rajkumar; Lacy	II	34	Len + Dex	56%	91%	90%	*Blood* 2005; ASH 2005
Niesvizky	II	42	Len + Dex + clarithro	51%	94%	86%	ASCO 2006
Rajkumar, E4A03 Arm A	III	223	Len + std-dose Dex	NA	NA	87%	ASCO 2007
Rajkumar, E4A03 Arm B	III	222	Len + low-dose Dex	NA	NA	96%	ASCO 2007
Palumbo	I/II	21	Len + MP (MP-R)	48%	81%	100%	EHA 2007

TABLE 54.10B Bortezomib Regimens in Newly Diagnosed Multiple Myeloma

Study	*Phase*	*N*	*Regimen*	*CR/VGPR*	*CR + PR*	*1-yr Survival*	*Reference*
Richardson	II	63	Bort	10%	40%	N/R	ASCO 2006
Jagannath	II	48	Bort ± dex	19%	90%	80%	*BrJH* 2005
Harousseau	II	48	Bort + dex	31%	66%	N/R	Haem 2006
Harousseau	III	79	Bort + dex	43%	82%	N/R	ASH 2006
Rosinol	II	40	Alternating Bort/Dex	22%	64%	N/R	ASCO 2007
Borrello	II	27	Bort + Thal	22%	82%	N/R	ASH 2006
Wang	II	36	Bort/TD (VTD)	19%	92%	N/R	ASH 2005
Mateos	I/II	60	MP-V	43%	89%	87%	*Blood* 2006
Oakervee	II	21	PAD	29%	95%	N/R	*BrJH* 2005
Orlowski	II	29	Bort + PLD	28%	79%	N/R	ASH 2006
Jakubowiak	II	28	Bort + PLD + Dex	53%	89%	N/R	ASH 2006
Barlogie	II	303	TT3 with bort	80%	90%	92%	ASCO 2007

N/R = Not reported.

WITH COMBINATION CT

- LOW INCIDENCE OF CR
- INCIDENCE OF SURVIVAL LESS

- HOW TO ACHIEVE
    - ? HIGH DOSE (MELPHALAN 140-200mg/m2)

Randomized Comparison of Conventional vs. High Dose therapy

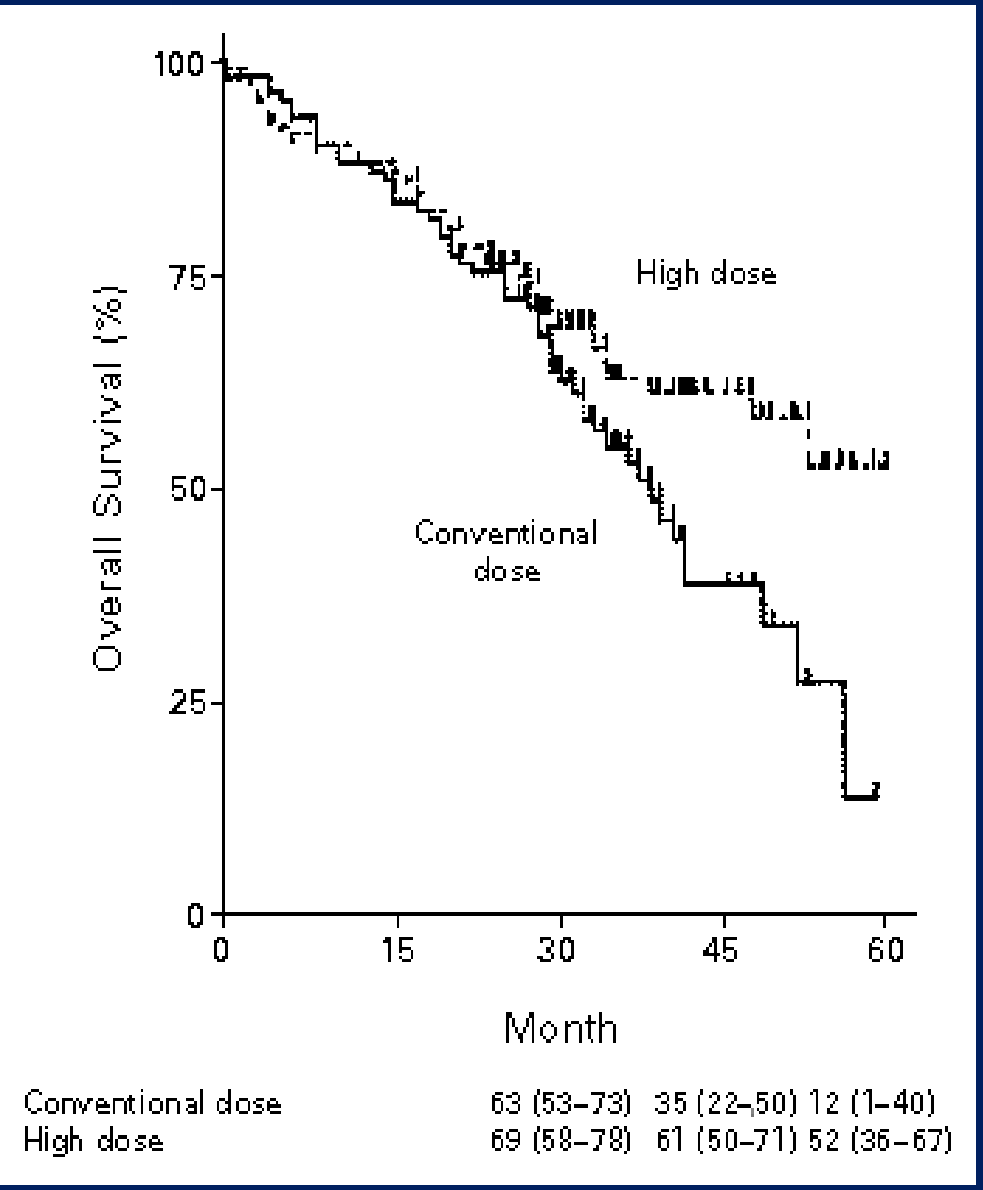
For newly diagnosed myeloma

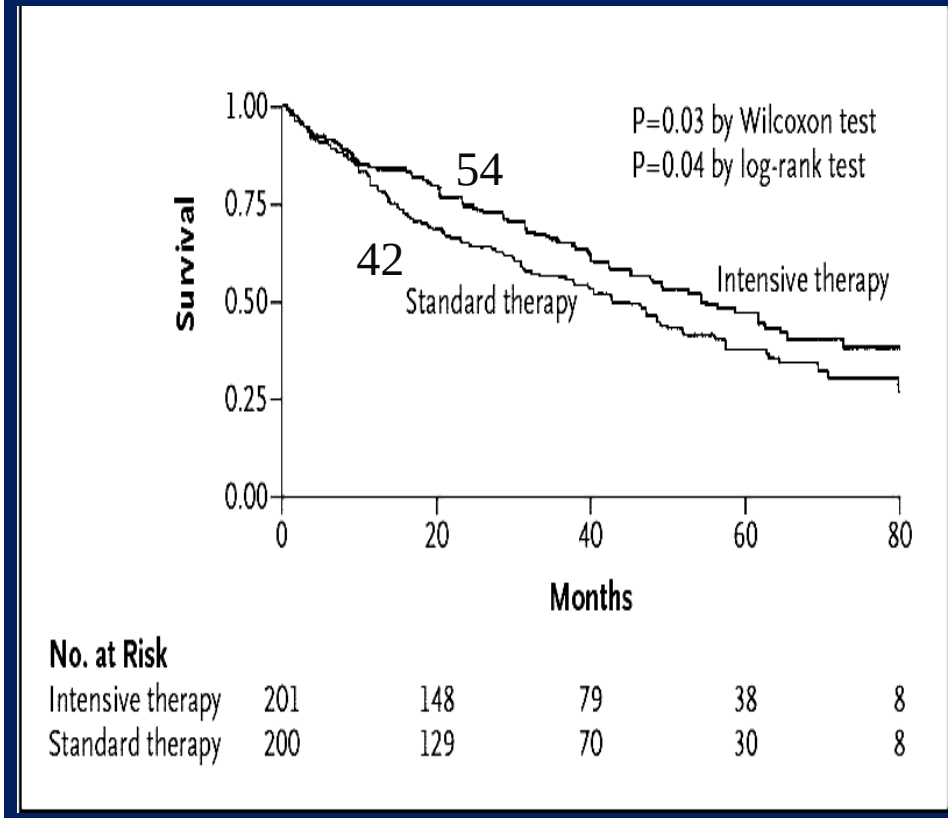
		Pat (n)	CR (%)	EFS (median, mo)	OS (median, mo)
Attal	Conv	100	5	18	37
	HDT	100	22	27	52%†
Barlogie	Conv*	116	--	22	48
	HDT	123	40	49	62
Fermand	Conv	91	--	13	24
	HDT\	94	--	39	64.6
Bladé	Conv	83	11	34.3	66.9
	HDT	81	30	42.5	67.4
Child	Conv	200	8.5	19.6	42.3
	HDT	201	44	31.6	54.1

*Conventional historical controls

Attal M et al. *N Engl J Med.* 1996;33
Barlogie B et al. *Blood.* 1997;89:789
Fermand J et al. *Blood.* 1998;92:3131
Lenhoff S et al. *Blood.* 2000;95:7
Bladé J *Blood.* 2001;98:815a
Child JA et al. *N Engl J Med.* 2003;348:1875

Transplant versus Conventional Chemotherapy





Attal M. *N Engl J Med* 1996; 335:97; Child J. *N Engl J Med* 2003; 348:1875

Single vs Double Autologous Transplantation

		CR (%)	EFS (median, mos)	OS (median, mos)
Fermand et al	Single Double	37 42	No difference	No difference
Attal et al	Single Double	49 63	25 30 p=.3	48 58 p=.01
Bologna 96	Single Double	35 48 p=NS	21.5 31	No difference*
Hovon 24	Single Double	13 28	20 22	55 50 ns

* Overall survival was improved for pts not achieving CR or near CR with first Auto

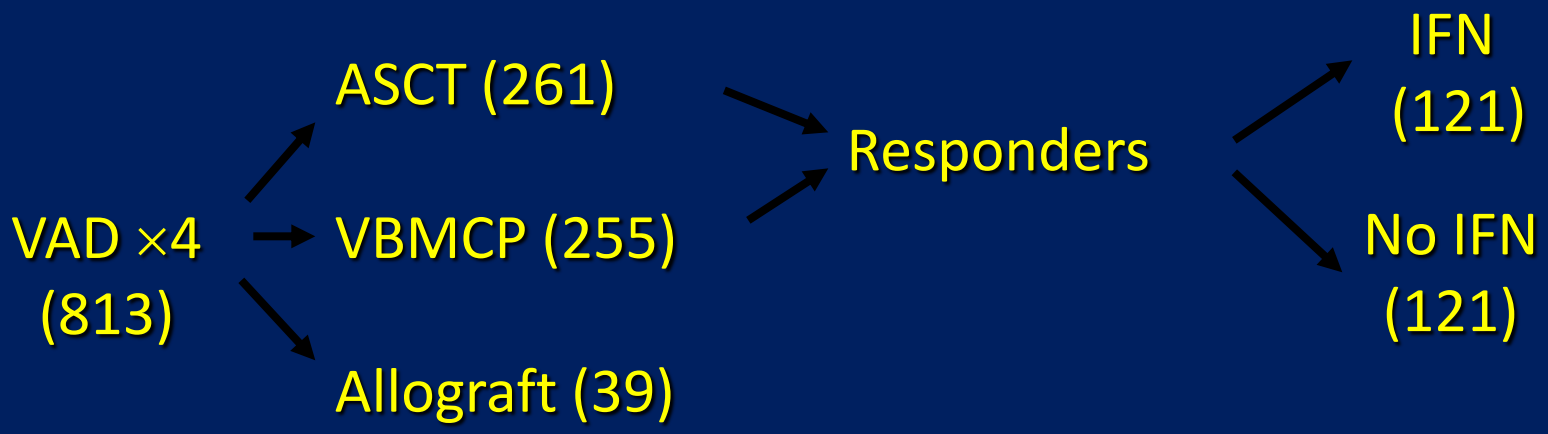
Fermand JP et al. Blood 2001; 98: 815a
Attal M, et al. NEJM 2003; 349: 2495
Fermand JP Mult Myeloma 2004, Torino Italy
Cavo M. Mult Myeloma 2004, Torino Italy
Sonneveld. Mult Myeloma 2004, Torino Italy
Sonneveld P et al. ASH 2004, abst 948

DESPITE IMPROVEMENT IN REMISSION,NO IMPROVEMENT IN SURVIVAL.
ALL PTS EVENTUALLY RELAPSE.

? CAN WE CONSIDER MAINTENANCE CHEMOTHERAPY

Maintenance with IFN after ASCT Comparable Survival in MM

In study of 899 patients, HDT (melphalan 140 mg/m^2 + TBI 12 Gy) vs standard dose VBMCP therapy showed no benefit for IFN maintenance



Crowley, et al. *Blood.* 2004;104 (part 1) [abstract 539]

Comparable Survival in MM With or Without IFN

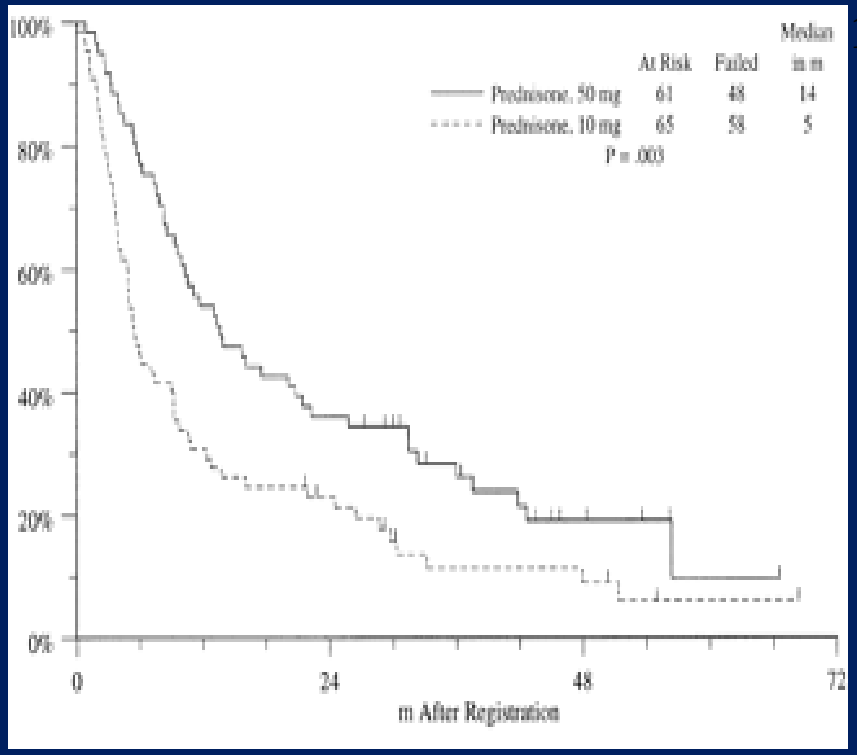
	CR	PR	PFS	OS
ASCT	17%	93%	25 mo *P*=0.05	62 mo *P*=0.8
VBMCP	15%	91%	21 mo	53 mo
+ IFN			23 mo	59 mo
– IFN			18 mo	74 mo

P=NS

52% VBMCP patients had salvage ASCT→ 59% PR (OS 30 mo) vs 23 mo w/o ASCT (*P*=0.05)

Crowley, et al. *Blood.* 2004;104 (part 1) [abstract 539]

Maintenance Prednisone



[1]

- After VAD or VAD-Quinine pts were randomized to maintenance prednisone, 10 mg qod vs 50 mg qod
- Progression free survival improved at 50 mg dose
  - 14 mos. vs. 5 mos.
- Overall survival also better
  - 37 mos. vs. 26 mos.

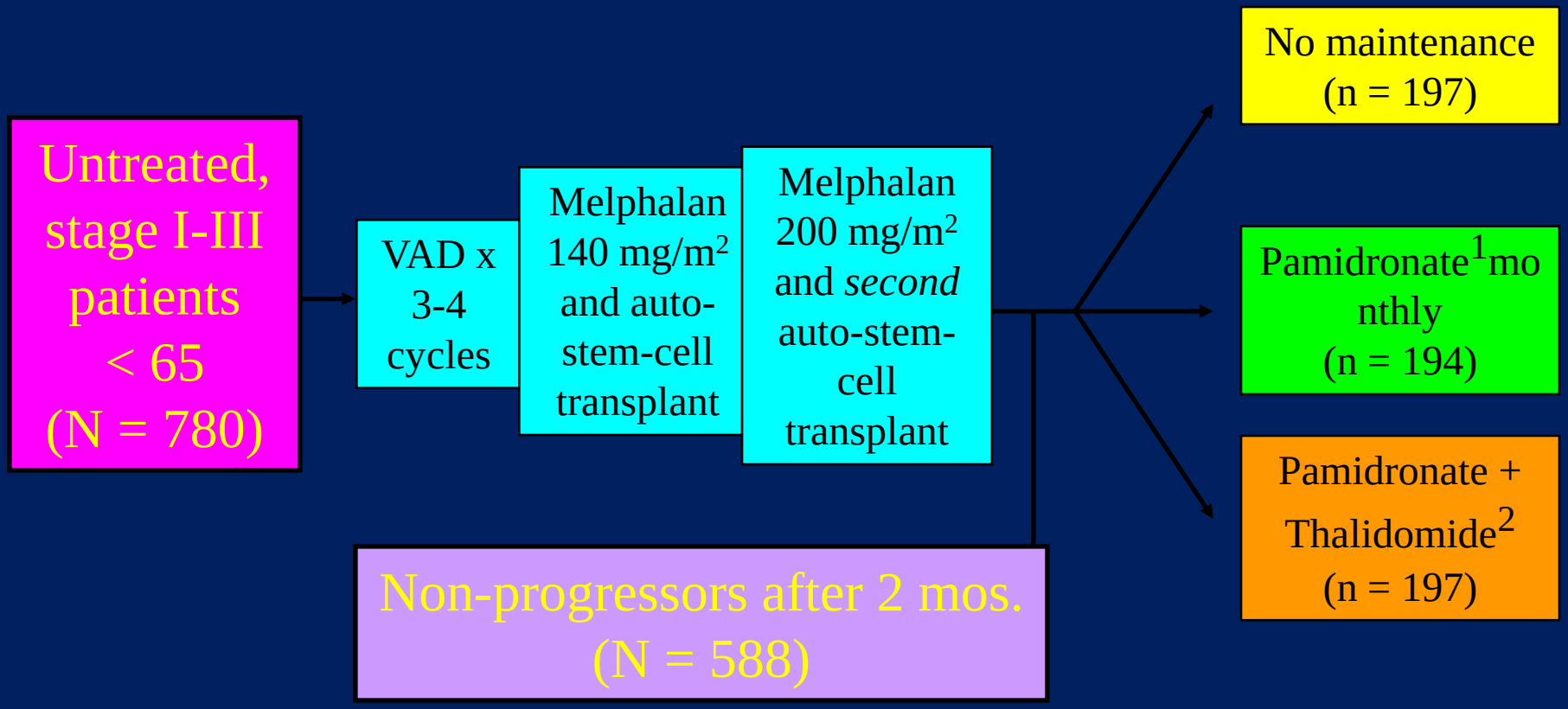
1. Berenson, JR et al. *Blood* 99:3163-3168, 2002.

Role of Maintenance Dexamethasone

- 307 pts
- Randomized trial following MP or M-Dex therapy to: Dex versus Observation
- Progression free survival better with maintenance Dex
- But no improvement in overall survival
- Further studies of maintenance therapy using novel agents needed

C. Shustik et al. Proc ASCO 2004

IFM 9920



[1]Pamidronate was given at 90 mg intravenously once monthly. [2]Thalidomide was given at 100 mg po qd.

Attal M, et al. *Blood.* 2004;104 (part 1) [abstract 535]

Maintenance With Thalidomide After ASCT for Myeloma

- Pam/Thal improved progression free, event free survival over Pam and controls

Response	Control	Pam	Pam/Thal	P Value
Median PFS, mos	27	28	> 38	.002
3-year PFS, %	34	37	56	.01
Overall survival, %	83%	78%	78%	NS

  - Significant benefits only if ≥90% response at randomization, and either del 13 or β_2m >3

Attal M, et al. *Blood.* 2004;104 (part 1) [abstract 535]

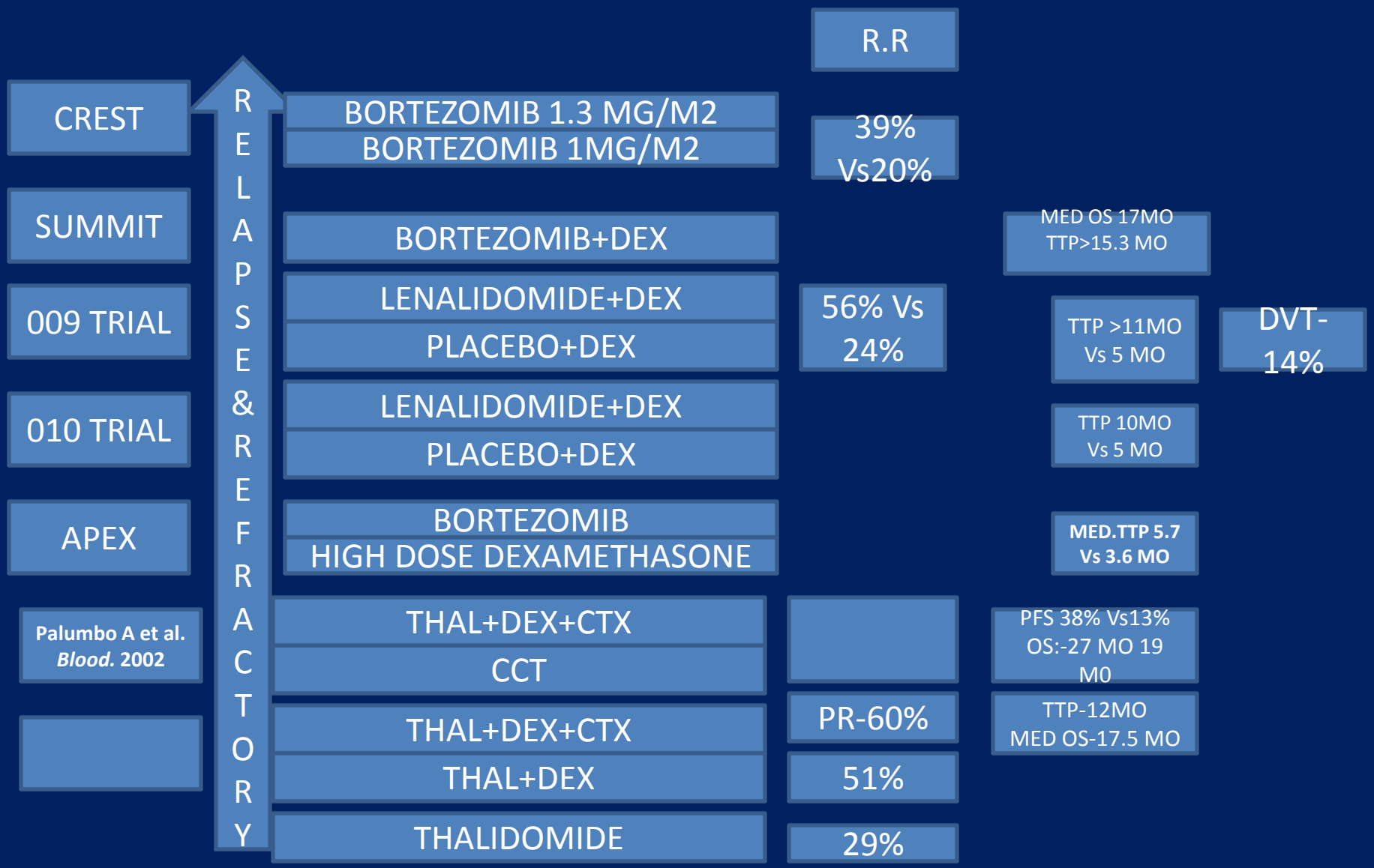

R.R
CREST
SUMMIT
009 TRIAL
010 TRIAL
APEX
Palumbo A et al. Blood. 2002
RELAPSE&REFRACTORY
BORTEZOMIB 1.3 MG/M2
BORTEZOMIB 1MG/M2
39% Vs20%
BORTEZOMIB+DEX
MED OS 17MO
TTP>15.3 MO
LENALIDOMIDE+DEX
PLACEBO+DEX
56% Vs 24%
TTP >11MO Vs 5 MO
DVT-14%
LENALIDOMIDE+DEX
PLACEBO+DEX
TTP 10MO Vs 5 MO
BORTEZOMIB
HIGH DOSE DEXAMETHASONE
MED.TTP 5.7 Vs 3.6 MO
THAL+DEX+CTX
CCT
PFS 38% Vs13%
OS:-27 MO 19 M0
THAL+DEX+CTX
PR-60%
TTP-12MO
MED OS-17.5 MO
THAL+DEX
51%
THALIDOMIDE
29%

TABLE 54.8A Thalidomide Regimens in Relapsed/Refractory Multiple Myeloma

Study	Phase	N	Regimen	Median # of Prior Tx	Median TTP (mo)	CR/VGPR	CR+PR	Ref.
Singhal	II	84	Thal	N/R	3.0 (EFS)	17%	25%	*NEJM* 1999
Barlogie	II	169	Thal	N/R	~5 (EFS)	20%	30%	*Blood* 2001
Palumbo	II	77	Thal + Dex	2	12	18%	41%	*Haematol* 2001
Dimopoulos	II	44	Thal + Dex	3	4.2	30%	55%	*Ann Oncol* 2001
Terpos	II	53	VMD-T	2	9.5	37%	60%	ASH 2006
Palumbo	I/II	30	VMP-T	3	N/R	43%	67%	ASH 2006

TABLE 54.9A Lenalidomide Regimens in Relapsed/Refractory Multiple Myeloma

Study	Phase	N	Regimen	Median # of Prior Tx	Median TTP (mo)	CR/VGPR	CR + PR	Reference
Richardson	I/II	24	Len	3	N/R	13%	30%	*Blood* 2002
Richardson	II	102	Len	>3	4.6	4%	17%	*Blood* 2006
Weber	III	171	Len + dex	3	11.1	13%	59%	ASCO 2006
Dimopoulos	III	176	Len + dex	3	11.3	15%	59%	ASCO 2006
Richardson	I	36	Len + Bort	5	N/R	6%	39%	ASH 2006
Richardson	I/II	28	Len + Bort + Dex	5	N/R	6%	31%	ASH 2006
Knop	I/II	31	Len + AD (RAD)	3	N/R	5%	84%	ASH 2006
Baz	I/II	52	Len + DVD (Len + PLD + Vd)	3	12	29%	75%	*Ann Oncol* 2006
Morgan	II	20	RCD (Len + Cyclophos + Dex)	4	N/R	27%	65%	*Br J Haemat* 2007

TABLE 54.10A Bortezomib Regimens in Relapsed/Refractory Multiple Myeloma

Study	Phase	N	Regimen	Median # of Prior Tx	Median TTP (mo)	CR/VGPR	CR + PR	Reference
Richardson	II	188	Bort	>3	~7	10%	27%	*NEJM* 2003
Richardson	III	333	Bort	2	6.2	4%	43%	*NEJM* 2005; ASH 2005
Richardson	III	132	Bort	1	7	6%	45%	ASCO 2006
Richardson	I/II	28	Len + Bort + Dex	5	N/R	6%	31%	ASH 2006
Berenson	I/II	35	Bort + Mel	3	8	6%	47%	*JCO* 2006
Harrousseau	III	324	Bort + PLD	≥2	9.3	36%	48%	ASH 2006; ASCO 2007
Chanan-Khan	II	23	Bort + PLD + Thal (VDT)	5	10.9	23%	65%	ASH 2006
Terpos	II	53	VMDT (Bort + Mel + Thal + Dex)	2	9.5	37%	60%	ASH 2006
Morgan	II	11	Bort + Cyclo + Dex	3	N/R	27%	64%	ASH 2006
Palumbo	I/II	30	Bort + MPT (VMPT)	3	N/R	43%	67%	ASH 2006
Baz	I/II	52	Len + DVD	3	12	29%	75%	*Ann Oncol* 2006

N/R = Not reported.

RADIATION

- TOTAL BODY IRRADIATION:-8 TO 12 Gy
  - FOR CONDITIONING BEFORE TRANSPLANT
  - IFM TRIAL 9502,IFM-M140-TBI,TORORNTO PROTOCOL:-INCREASED
- HEMI BODY IRRADIATION:-5 TO 8Gy
  - FOR PALLIATION IN CHEMOREFRACTORY PTS.NO ROLE OF SEQUENTIAL HEMIBODY RT AS SYSTEMIC TREATMENT
- LOCAL EBRT FOR PALLIATION
  - RELIEF OF SPINAL CORD COMPRESSION
  - 40 % MM PTS REQUIRE PALLIATIVE RT TO RELIEVE FROM BONE PAIN
  - ROLE OF RT IN PREVENTING IMPENDING PATH FRACTURE IS UNCLEAR.(LESION AT HIGH RISK OF PATH # SHOULD UNDERGO SURGERY FOLLOWED BY RT FOR RESIDUAL DISEASE.)
- RADIOIMMUNOTHERAPY APPROACH
  - 153 SAMARIUM-ETHYLENE DIAMINE TETRAMETHYLENE PHOSPHONATE,166 HOLMIUM-DOTMP.
  - HETEROGENEITY OF UPTAKE IN SKELETON

IFM95 Mel 200 vs Mel-TBI

	Mel-TBI	Mel 200
N	147	147
Deaths	3.6%	0%
CR	29%	35%
CR+VGPR	43%	55%
EFS	ND	ND
OS	Worse	Better

RADIATION FOR PAIN

- LOCAL FIELD,NOT THE WHOLE BONE
- NO DIFFERENCE IF WITH CT/WITHOUT CT
- LONGER FRACTIONATED REGIMEN-BETTER PAIN CONTROL THAN SINGLE FRACTION
- EXTENT OF DISEASE BY MRI IN PLASMACYTOMA
- SPINAL PLASMACYTOMA:-2 VERTEBRA ABOVE AND 2 VERTEBRA BELOW
- NO NECESSITY TO INCLUDE REGIONAL L.N IN SOLITARY PLASMACYTOMA
- EXTRAMEDULLARY PLASMACYTOMA THE REG.L.N INVOLVEMENT INCIDENCE:-10-20%:- CONTROVERSIAL TO GIVE PROPHYLACTIC RT TO REG.L.N
- RT FIELD:-2 TO3 CM FROM GROSS TUMOR
- DOSE:- OSSEOUS AND EXTRA OSSEOUS LESION:- 40 TO 45GY
    - PAIN RELIEF:- 10-25 Gy(RESPONSE RATE:-96%)
- NO DOSE RESPONSE AFTER 10 Gy

FOLLOW UP

- ***MGUS***:-REPEAT PROTEIN STUDIES APPROXIMATELY EVERY 6 MO FOR 2-3 YRS,ANNUALY THER AFTER.
- ***SMM***:-EVERY 3 MOWITH SERUM PROTEIN ELECTROPHORESIS ,BLOOD COUNT AND CREATININE AND SKELETAL SURVEY AT 12 MO INTERVAL.
- ***EVIDENCE OF PROGRESSIVE DISEASE***:-
  - INCREASE M PROTEIN
  - DECLINING HEMOGLOBIN
  - INCREASE CREATININE
  - LYTIC LESION
  - RECURRENT INFECTION

Management of Myeloma

- Supportive care (cont..)
  - Hypercalcemia
    - Hydration
    - Corticosteroids
    - Bisphosphonates
  - ↑ serum creatinine
    - Hydration
    - Disease-directed therapy
    - Avoid NSAIDs

Management of Myeloma

- Supportive care (cont..)
  - Infections
    - Appropriate antimicrobials
  - Anemia
    - Red cell transfusions
    - Erythropoietin
  - DVT prophylaxis & treatment
    - Aspirin, LMWH, warfarin
  - Other co-morbid conditions
    - Heart, diabetes mellitus, etc

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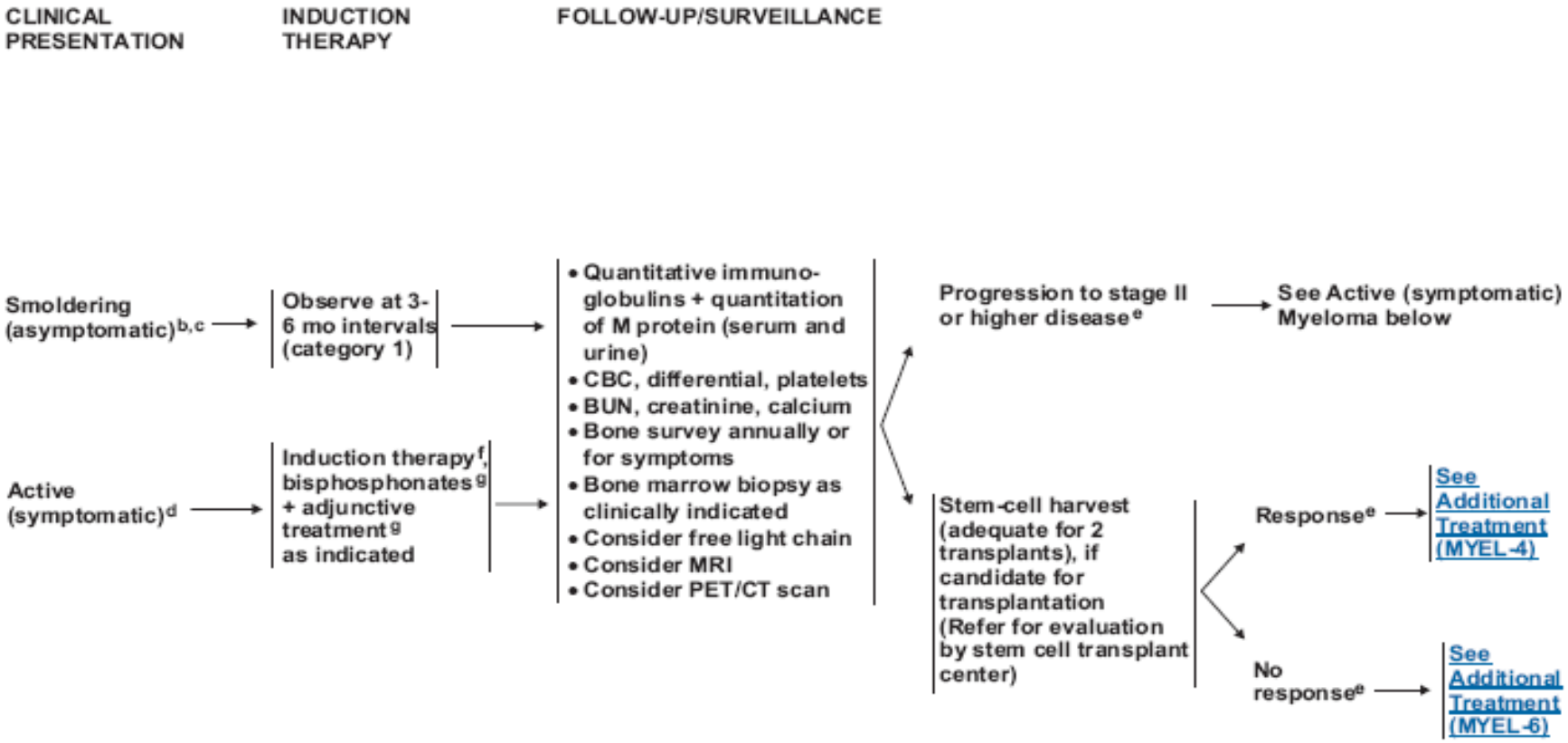

[a] See Staging Systems for Multiple Myeloma (MYEL-A).
[b] See Smoldering (Asymptomatic) Myeloma (MYEL-B).
[c] Includes Durie-Salmon Stage I myeloma.
[d] See Active (Symptomatic) Myeloma (MYEL-B).
[e] See Response Criteria for Multiple Myeloma (MYEL-C).
[f] See Myeloma Therapy (MYEL-D).
[g] See Adjunctive Treatment (MYEL-E).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

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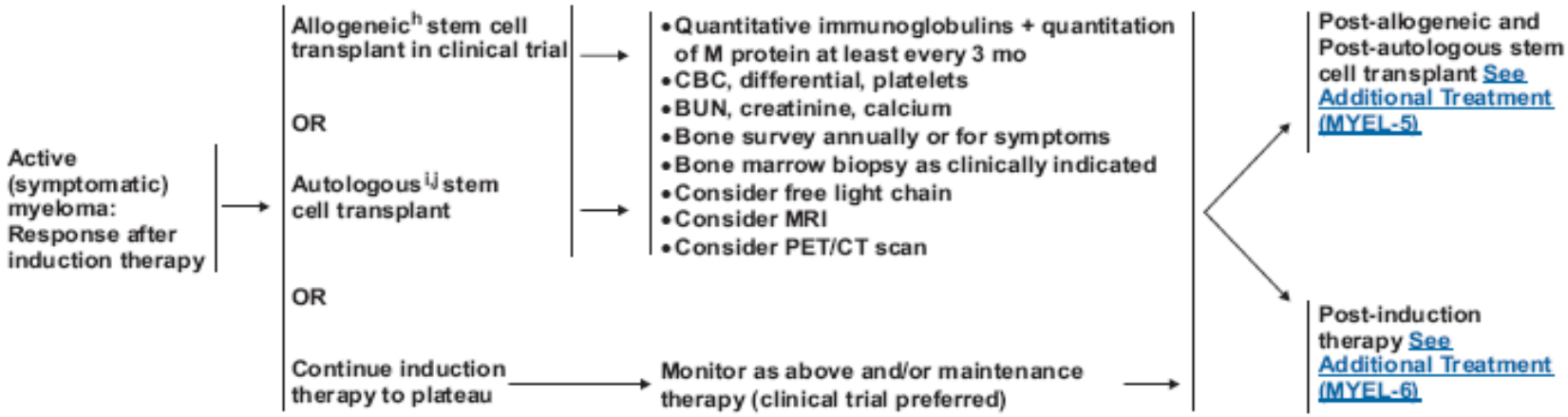
FOLLOW-UP/SURVEILLANCE



[h] A prospective trial by Bruno, et al. NEJM 2007;356:1110-1120, found improved survival for patients receiving an autologous transplant followed by non-myeloablative allograft compared to patients who received tandem autologous grafts. The IFM trial (99-03) by Garban et al, Blood 2006; 107:3474, reported no overall survival or progression free survival with autologous transplant followed by mini allograft in high-risk myeloma patients. Allogeneic stem cell transplant may include nonmyeloablative (mini) following autologous stem cell transplant or fully myeloablative on a clinical trial (off-trial category 3). Current data do not support miniallografting alone.

[i] Single autologous transplantation: Category 1 evidence supports proceeding straight after induction therapy to high dose therapy and stem cell transplant versus saving the stem cell transplant for salvage therapy. Evidence suggests equivalent overall survival although progression free survival can be prolonged by an early transplant. Fermand JP, Katsahian S, Divine M, et al. High dose therapy and autologous blood stem cell transplantation compared with conventional treatment in myeloma patients aged 55 to 65 years: Long term results of a randomized control trial from the Group Myelome-Autogreffe. J Clin Oncol 2005;23:9227-9233.
Barlogie B, Kyle RA, Anderson KC, et al. Comparable survival of patients with multiple myeloma treated with autotransplant-supported melphalan - TBI or standard VBMCP consolidation and no role of interferon maintenance: final results of US Intergroup Trial S9321. J Clin Oncol 2006;929-936.

[j] Renal dysfunction and advanced age are not contraindications to transplant.

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ADDITIONAL TREATMENT

Post-allogeneic stem cell transplant:

- Progressive disease[e] → Salvage therapy[f] on or off clinical trial or Donor lymphocyte infusion
- Response[e] or stable disease → Observe or maintenance therapy[f] → Progressive disease[e] → Salvage therapy[f] on or off clinical trial or Donor lymphocyte infusion

Post-autologous stem cell transplant:

- Refractory disease[e] → Salvage therapy[f] on or off clinical trial or Allogeneic stem cell transplant on clinical trial[k] (category 3 for conventional vs clinical trial)
- Stable disease[e] → Observe or Second tandem transplant or Maintenance therapy[f] → Progressive disease[e] → Salvage therapy[f] on or off clinical trial or Allogeneic stem cell transplant on clinical trial[k] or Additional autologous stem cell transplant on clinical trial (category 2B)

[e] See Response Criteria of Multiple Myeloma (MYEL-C).
[f] See Myeloma Therapy (MYEL-D).
[k] Allogeneic stem cell transplant may include nonmyeloablative (mini) following autologous stem cell transplant or fully myeloablative on a clinical trial (off-trial category 3). Current data do not support miniallografting alone.

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ADDITIONAL TREATMENT

Post-induction therapy:

Relapse disease[e] or progressive disease

- **Transplant candidate[i]** → **Autologous stem cell transplant (category 1)** → **Progressive disease[e]** → **Salvage therapy[f] on or off clinical trial**
  or
  Allogeneic stem cell transplant on clinical trial[k]
  or
  Additional autologous stem cell transplant on clinical trial (category 2B)
- **Non-transplant candidate** → **Salvage therapy[f] on or off clinical trial** → **Palliative care**
  (See NCCN Palliative Care Guidelines)

Active (symptomatic) myeloma: Progressive disease[e] →

Autologous stem cell transplant on or off clinical trial[i]

or

Salvage therapy[f] on or off clinical trial

or

Allogeneic stem cell transplant on a clinical trial[k]

[e] See Response Criteria for Multiple Myeloma (MYEL-C).

[f] See Myeloma Therapy (MYEL-D).

[k] Allogeneic stem cell transplant may include nonmyeloablative (mini) following autologous stem cell transplant or fully myeloablative on a clinical trial (off-trial category 3). Current data do not support miniallografting alone.

[i] Single autologous transplantation: Category 1 evidence supports proceeding straight after induction therapy to high dose therapy and stem cell transplant versus saving the stem cell transplant for salvage therapy. Evidence suggests equivalent overall survival although progression free survival can be prolonged by an early transplant.
Fermand JP, Katsahian S, Divine M, et al. High dose therapy and autologous blood stem cell transplantation compared with conventional treatment in myeloma patients aged 55 to 65 years: Long term results of a randomized control trial from the Group Myelome-Autogreffe. J Clin Oncol 2005;23:9227-9233.
Barlogie B, Kyle RA, Anderson KC, et al. Comparable survival of patients with multiple myeloma treated with autotransplant-supported melphalan - TBI or standard VBMCP consolidation and no role of interferon maintenance: final results of US Intergroup Trial S9321. J Clin Oncol 2006;929-936.

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MYELOMA THERAPY[1,2,3,4]

- Exposure to myelotoxic agents (including alkylating agents and nitrosoureas) should be limited to avoid compromising stem-cell reserve prior to stem-cell harvest in patients who may be candidates for transplant.

- Primary induction therapy for transplant candidates:
  - Bortezomib/dexamethasone (category 1)
  - Bortezomib/doxorubicin/dexamethasone (category 1)
  - Bortezomib/lenalidomide[5]/dexamethasone (category 2B)
  - Bortezomib/thalidomide/dexamethasone (category 1)
  - Dexamethasone (category 2B)
  - Liposomal doxorubicin/vincristine/dexamethasone (DVD) (category 2B)
  - Lenalidomide[5]/dexamethasone (category 1)
  - Thalidomide/dexamethasone (category 2B)

- Primary induction therapy for non-transplant candidates:
  - Dexamethasone (category 2B)
  - Lenalidomide/low-dose dexamethasone (category 1)
  - Liposomal doxorubicin/vincristine/dexamethasone (DVD) (category 2B)
  - Melphalan/prednisone (MP)
  - Melphalan/prednisone/bortezomib (MPB) (category 1)
  - Melphalan/prednisone/thalidomide (MPT) (category 1)
  - Thalidomide/dexamethasone (category 2B)
  - Vincristine/doxorubicin/dexamethasone (VAD) (category 2B)

- Maintenance therapy:
  - Interferon (category 2B)
  - Steroids (category 2B)
  - Thalidomide (category 1) ± prednisone (category 2B)

- Salvage:
  - Bendamustine (category 2B)
  - Bortezomib[6] (category 1)
  - Bortezomib/dexamethasone
  - Bortezomib/lenalidomide/dexamethasone (category 2B)
  - Bortezomib/liposomal doxorubicin[6] (category 1)
  - Cyclophosphamide-VAD
  - Dexamethasone
  - Dexamethasone, cyclophosphamide, etoposide, and cisplatin (DCEP)
  - Dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, and etoposide (DT-PACE)
  - High-dose cyclophosphamide
  - Lenalidomide/dexamethasone (category 1)
  - Lenalidomide
  - Repeat primary induction therapy (if relapse at > 6 mo)
  - Thalidomide
  - Thalidomide/dexamethasone

[1]Selected, but not inclusive of all regimens.
[2]Treatments are listed alphabetically and do not imply preference.
[3]Consider herpes zoster prophylaxis for patients treated with bortezomib.
[4]Prophylactic anticoagulation recommended for patients receiving thalidomide-based therapy or lenalidomide with dexmethasone.
[5]Consider harvesting peripheral blood stem cells prior to prolonged exposure to lenalidomide.
[6]Bortezomib/liposomal doxorubicin is preferred to bortezomib single agent.

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Return to Primary Treatment (MYEL-2)

Challenges in Management

- Currently incurable in most patients
- DESPITE HIGH RESPONSE RATE,ALL PTS EVENTUALLY RELAPSE.
- IMOROVE SURVIVAL WITH SCT TRIAL WITH HIGH DOSE THERAPY
- Chemotherapy response rates = 50% to 70%
  - Long-term complete responses = rare
  - Median survival with standard therapy = 3 years
- Stem cell transplant prolongs survival, but not curative
- Treatment of relapse
  - No standard therapy
  - Existing options inadequate
- New treatment options needed

THANK YOU